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			EXAMINER LUCAS, ZACHARIAH	
			ART UNIT 1648	PAPER NUMBER

DATE MAILED: 11/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/981,636

Applicant(s)

MARKS ET AL.

Examiner

Zachariah Lucas

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-72 is/are pending in the application.
- 4a) Of the above claim(s) 4 and 16-72 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☒ Claim(s) 1-3 and 5-15 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12-17-02, 7-11-03.
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date. 10-27-04.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, subgroup B, and the species represented by the election of the His tag epitope tag and the fluorescent label as a reporter in the replies filed on May 10, 2004, and August 27, 2004 is acknowledged. The traversal is on the ground(s) that the Examiner has improperly imposed a restriction requirement among different inventions that fall within a single claim, and that such is contrary to the law which requires the Office not impose a rejection on a claim for reading on multiple inventions. This is not found persuasive because the Office is not refusing to examine the claims to their full scope. As was noted in paragraph number 12 of the Restriction Requirement mailed on March 9, 2004, the Office acknowledged that certain claims were generic to the multiple inventions, and that the generic claims would be examined along with the elected invention. Although it is improper to reject a claim for reading among several inventions, it is not improper to restrict among several independent or distinct inventions. See e.g., 35 U.S.C. 121, and 37 CFR 1.142 (indicating that the Office may restrict among "two or more inventions", and being silent as to the propriety of restriction within a claim. As there has been no rejection of the claims for reading on multiple inventions, and as the Applicant has pointed out any supposed errors in the restriction requirement (other than that, in Applicant's view, no restriction should have been made), the restriction requirement is maintained.

The requirement is still deemed proper and is therefore made FINAL.

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2. Claims 4, and 16-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on May 10, 2004, and August 27, 2004.

3. Currently, claims 1-3, and 5-15 are under examination to the extent that they read on the elected inventions, or are generic thereto.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on December 17, 2002, and on July 11, 2003, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

5. It is noted that, although each of the reference listings of the information disclosure statements indicated above indicates that the listing page present is the first of two pages, only one page listing references was present in the file for either of the statements. It is also noted that the Applicant confirmed in an interview on October 27, 2004, that only one page of references was submitted in each instance.

6. No copy of the Matzku et al. reference, cited in the July 11, 2003 IDS, was found in among references submitted with the IDS. This reference has therefore not been considered.

Claim Objections

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7. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This claim purports to further limit the method of claim 1. Claim one involves a methods of identifying an internalizing antibody, including a step of contacting a cell "with a reporter non-covalently coupled to" the antibody. However, claim 2 reads on methods wherein the contacting involves two steps; first, the contacting of a cell with an antibody comprising an epitope tag, and second contacting the cell with a reporter comprising an moiety that binds the epitope tag. Because claim 1 appears to require that the cell is contacted with an antibody already coupled to a reporter, and because claim 2 reads on methods wherein the antibody is not coupled to the reporter until after it has bound the cell, claim 2 does not appear to be further limiting of the method of claim 1. Rather, claims 1 and 2 describe alternative embodiments of the claimed methods.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-3, 5-10, and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of identifying an antibody or fragment thereof (collectively referred to as "antibody") comprising the steps of i) contacting a cell with a reporter (label) non-covalently coupled to the antibody,

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ii) dissociating the reporter from the antibody and removing the reporter from the surface of the cell, and

iii) detecting the presence of the reporter in the cell.

It is not clear how the reporter is being detected inside the cell, or how the reporter determines that the ligand is internalized, where the reporter is dissociated from the ligand while still on the cell surface. It is suggested that the claim be amended to read on a method wherein step ii) comprised - - dissociating reporter from antibody bound to the surface, but not internalized into the cell, and removing the dissociated reporter from the surface of the cell- -; and wherein step iii) comprises - - detecting the presence of reporter coupled to internalized ligand within said cell." Support for the additional language may be found from the teachings in the originally filed claim 1, in combination with the teachings on pages 6-7 (relating to a method for distinguishing between ligand bound to the surface and internalized, from ligand internalized into the cell), and from what one of ordinary skill in the art would have understood from these teachings.

Clarification of the claim language is required.

10. Claims 1- 3, and 5-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are rejected because it is unclear what is meant by the step "contacting said cell with a reporter non-covalently coupled to a ligand." This is the second step of the method of claim 1. The rejection is based on the apparently contradictory language in this claim, and the language of claim 2. Claim 1 appears to require that the cell is simultaneously contacted with both the antibody and the reporter, which two components are

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themselves non-covalently coupled. Claim 2 indicates that the contacting step of claim 1 may also include embodiments wherein cell is contacted, separately and successively, first with the antibody and then the reporter. Because the language of these two claims appear to describe mutually exclusive embodiments, it is not clear how claim 2 further limits claim 1. The scope of the inventions falling within claim 1 is therefore unclear.

11. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites the limitation "said epitope tag." There is insufficient antecedent basis for this limitation in the claim. The claim from which this claim depends does not introduce an epitope tag. It is therefore unclear what epitope tag is being referred to.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1, 3, 5-7, 10, 13, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,794,128. The present claims are drawn to methods of identifying ligands internalized into cells, wherein the ligands may be an antibody or fragment thereof, may be produced as part of a phage display library, and may be non-covalently coupled to a reporter.

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The claims of the copending application are drawn to methods of identifying internalized antibodies of antibody binding moieties, wherein the binding moieties are part of a phage display library and wherein the phages include a reporter. While the ligands of the copending application are covalently bound to the phage, they do not appear to be covalently bound to the reporter moieties of the phage (i.e. DNA or RNA encoding a reporter protein). Thus, the current claims are generic to the claims of the copending application. The claims of the patent therefore anticipate the indicated claims of the present application.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claims 1, 3, 10, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein et al. (U.S. Patent 6,251,392- of record in the December 2002 IDS) in view of the

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teachings of Hurwitz et al. (PNAS 92:3353-57- of record in the July 2003 IDS) and U.S. Patent 5,296,348 (the '348 patent, issued to Rakowicz-Szulczynska). These claims are drawn to methods of identifying antibodies that are internalized into cells through non-covalent conjugation of the antibodies to a reporter, exposing the conjugate to a cell, dissociating reporter bound to antibody on the surface of the cell, and detecting reporter present inside the cell.

Hein teaches methods of identifying internalizing ligands into cells through conjugation of the ligand to a reporter, exposing the conjugate to a cell, and detecting the reporter inside the cell. See e.g., column 7, lines 35-62. The reference teaches that antibodies may be used as an alternative to peptides as internalizing ligands are antibodies, and fragments or derivatives thereof. See columns 11-12. The reference suggests the use of such internalizing ligands and antibodies for the delivery of therapeutic agents into cells, including for the delivery of biological agents to cancers. Columns 16-17. While the reference does not teach how the reporter is conjugated to the antibodies, it does teach that the biological agents may be conjugated to the identified agents through covalent, or non-covalent means. Thus, it would have been obvious to those in the art to use either of such means for the attachment of the reporters to the antibodies tested for internalization. The reference therefore teaches the identification of internalizing antibodies, including antibodies internalized into cancer cells, for later use as carriers of therapeutic agents. However, the reference does not teach a step involving the dissociation of the reporter to surface bound antibodies.

Each of Hurwitz and the '348 patent also teaches methods for the identification of internalizing antibodies. The teachings of the '348 patent indicates that it is necessary to distinguish between the antibodies that are internalized, and those that are merely bound to the

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cell surface. See e.g., abstract (noting that the patent is drawn to methods of distinguishing internalizing antibodies from other antibodies that merely bind to the surface). Hurwitz provides a means for identifying antibodies that are internalized through the removal of antibodies bound to the cell surface, and then detection of a reporter conjugated to the antibodies tested within the cell. Pages 354 (left column "Internalization of Antibodies," describing a step of washing or proteolysis of surface-exposed molecules prior to the detection step). It would therefore have been obvious to those in the art to have used such a washing step to distinguish between the internalized and surface bound antibodies in the method suggested by Hein. It would appear that such a method would also inherently result in the dissociation of the reporter from the antibody where the reporter and antibody are non-covalently bound. Additionally, because it is clear from the references that the reporter is the moiety being detected, it would also have been obvious to those in the art that the internalized inside the cell could be distinguished from those merely bound to the surface by dissociating the ligand on surface bound antibodies. This is because it would have been apparent that, if the reporter on the surface bound antibodies is no longer present. Evidence that those in the art would have understood this is present in the Tsaltas et al reference (of record in the July 2003 IDS). See, pages 8-9 (teaching that the effects of dissociation from conjugated antibody from the target antigen, and of a label from the antibody bound to the antigen would have similar effects with respect to the results on an immunoassay using the antibody-label conjugate).

Because the purpose of such a method is for the identification of an antibody that can be used as a carrier for drug delivery, it would have been obvious to those in the art to additionally isolate the antibody. Further, and for the same reasons, having isolated the antibody, it would

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also have been obvious to determine its sequence, or the sequence of an encoding nucleic acid, such that the antibody could be produced for later use. Thus, the teachings of the art render obvious the methods described by the indicated claims.

16. Claims 2 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, and further in view of Burmer et al. (U.S. Patent 6,087,103) and of Collins (U.S. Patent 5,770,422) and Freed et al. (U.S. Patent 5,597,719). As indicated above, claim 2 reads on methods such as those described above, except that that the cell is contacted with two separate compounds, the first is the antibody comprising an epitope tag, and the second is a reporter comprising a moiety that binds the epitope tag. The teachings of the Hein, Hurwitz, and the '348 patent have been described above. While these references teach the detection of antibodies using a reporter, they do not teach that the antibody and the reporter may be separate compounds when administered to the cell, or the use of an epitope tag to link the reporter and the antibody.

Burmer teaches methods for the identification of target-ligand interactions. Among the relevant teachings provided in the reference are means of conjugating labels to ligands. Columns 12-13. The reference teaches that a tag may be conjugated to the ligand, and that a detectable moiety may then be conjugated to the tag. Col. 12, lines 15-25, and 46-60. While the reference does not specifically identify epitope tags as a useful tags, such would have been obvious from the teachings of Collins and Freed. Each of these later references teaches means for detection of proteins that were known in the art, and that could be applied to the detection of internalizing antibodies. Both Collins (column 8-9) and Freed (column 8, lines 6-11) indicate that the use of

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an epitope tag conjugated to the target, in combination with antibodies directed to that tag, may be used for indirect detection of the target protein. From these teachings, it would have been obvious to those in the art to use attach an epitope tag to the antibody to be screened as suggested by Hein, Hurwitz, and the '348 patent, and to use an anti-epitope tag antibody conjugate as an indirect label for the internalizing antibody. Those in the art would have been motivated to use such a label because its use was known in the art, and because the ability of the antibody to carry an additional large protein into the cell would have provided additional evidence of the antibodies utility as a drug-carrier (the utility of the antibodies suggested by Hein and the '348 patent).

17. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, and further in view of Barbas et al., PNAS 88:7978-7982) and Ward et al. (J Immunol Methods 189: 73-82). These claims are drawn to methods wherein the antibodies tested for internalization are produced by a filamentous phage display library. The previously described references do not teach the production of the antibodies to be tested through a phage display library. However, Barbas demonstrates that it was known in the art to produce phage display libraries that express antibody libraries. Additionally, Ward teaches that the antibodies may be isolated from the libraries through incorporation of an enzymatic cleavage site in the recombinant phage protein comprising the antibody. It would therefore have been obvious to those in the art to produce antibodies to be tested in the methods described above through isolation of a library of antibodies from a phage display library as

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described in the Barbas and Ward references. The combined teachings of these references therefore render the indicated claims obvious.

18. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, further in view of the teachings of Plant et al. (U.S. Patent 5,389,523- of record in the July 2003 IDS) and Szoka et al. (U.S. Patent 6,593,308). Claims 9-11 are drawn to embodiments of the previously described claims wherein the antibody is coupled to the reporter through a His-tag, and to embodiments wherein the reporter is a liposome comprising nitrilotriacetic acid (NTA). As indicated above, Hein, Hurwitz, and the '348 patent intended that the antibodies disclosed therein would act as carriers for therapeutic drugs, including for delivery to cancer cells. However, the references do not teach the use of a His-tag to conjugate the antibody to a liposome.

Plant teaches the coupling of proteins or peptides to liposomes to improve the detectability of protein interactions in immunoassays. Column 2 lines 1-34. In particular, the reference teaches the attachment of antibodies, or fragments thereof, to liposomes comprising a detectable moiety for use in immunoassays. From these teachings, it would have been obvious to those in the art to attach the antibodies of Hein to the liposomes of Plant for use in the methods of detection. However, Plant does not teach the use of the His-tag, or the non-covalent joining of the antibody with the liposome.

Szoka teaches a composition for the delivery of drugs comprising a cell ligand attached to a liposome carrying the drug to be delivered. The ligand is intended to target the liposome to cancer cells. Columns 1-2. The reference teaches that the ligand may be attached to the liposome

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through fusion of the antibody to a His-tag, which binds to a NTA molecule on the liposome.

Columns 13-14. From these teachings, it would have been obvious to those in the art to attach the antibodies to be tested as suggested by Hein, Hurwitz, and the '348 patent to a liposome as suggested by Szoka. Because the conjugates of Szoka are disclosed as having the intended use of the internalizing antibodies of Hein, it would have been obvious to those in the art to use the liposomes of Szoka, rather than those of plant, in methods for the identification of antibodies that internalize into cancer cells. It would have been obvious to those in the art to substitute the antibodies to be tested for the ligand of Szoka, and to have use the liposome of Szoka to carry the detectable moiety as suggested by Plant.

The motivation for the use of the Szoka liposome (and method of conjugation) is that, as Szoka discloses their conjugate as having the same anti-cancer utility as suggested for the antibodies of Hein, those in the art would have been motivated to replace the ligand of Szoka with the antibody to determine its ability to act as a functional equivalent. However, as both liposomes are intended to carry molecules, it would also have been obvious that the liposome of Szoka would have improved the detectability of the antibodies for the same reasons as indicated with respect to the Plant liposome. Thus, the combined teachings of the references would have rendered the claimed inventions obvious to one of ordinary skill in the art.

19. Claims 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, further in view of Stewart et al. (U.S. Patent 6,087,452). Claim 9 read on a method wherein the reporter is linked to the antibody through a His-tag. Claim 12 reads on embodiments wherein the reporter is non-covalently bound to the

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antibody through a covalent linkage to protein A, which in turn non-covalently binds the antibody. The teachings of Hein, Hurwitz, and the '348 patent have been described above. These references do not teach the use of a polyhistidine/protein A linker to non-covalently join the reporter to the antibody. However, Stewart teaches that the use of such a linker for the attachment of antibodies to another compound. Column 12, lines 27-27. While Stewart teaches that use of such a linker for the attachment of the antibody to a substrate, it would have been obvious to those in the art that the linker could be used for the attachment of the antibody to any composition comprising an appropriate metal-ion.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1, 3, 5-7, 10, 13, and 14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-12, 23-31, 33-36 of U.S. Patent 6,794,128. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present application are generic to the claims of the copending application. The present claims are drawn to methods of identifying ligands

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internalized into cells, wherein the ligands may be an antibody or fragment thereof, may be produced as part of a phage display library, and may be non-covalently coupled to a reporter.

The claims of the copending application are drawn to methods of identifying internalized antibodies of antibody binding moieties, wherein the binding moieties are part of a phage display library and wherein the phages include a reporter. While the ligands of the copending application are covalently bound to the phage, they do not appear to be covalently bound to the reporter moieties of the phage (i.e. DNA or RNA encoding a reporter protein). Thus, the current claims are generic to the claims of the copending application.

22. Claims 1, 3, 5-7, 10, 13, and 14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, and 12-15 of U.S. Patent No. 10/855,755. Although the conflicting claims are not identical, they are not patentably distinct from each other for substantially the same reasons as indicated with respect to the claims of U.S. patent 6,794,128 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

23. No claims are allowed.

24. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Hellstrom et al., U.S. Patent 5,980,896. This reference teaches the use of internalizing antibodies for the treatment of cancers. Abstract, columns 2-3. However, while the

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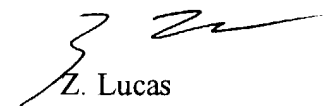
reference teaches a need in the art for such antibodies, the reference teaches an alternative method for the identification of such antibodies. See, column 61, esp., lines 35-55.

Dietrich et al., PNAS 92: 9014-18. This reference teaches the use of a histidine tag to bind to NTA as a linker among biological molecules. The reference is therefore considered relevant to the claimed invention, in particular to the inventions of claim 11.

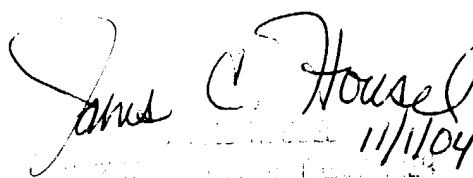
25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Z. Lucas
Patent Examiner



James C. Housel
11/1/04
11/1/04